



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,238	09/25/2003	Rudi Rossau	12546.2USC4	8516
23552	7590	06/01/2007	EXAMINER	
MERCHANT & GOULD PC			MYERS, CARLA J	
P.O. BOX 2903			ART UNIT	PAPER NUMBER
MINNEAPOLIS, MN 55402-0903			1634	
MAIL DATE	DELIVERY MODE			
06/01/2007	PAPER			

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/672,238	ROSSAU ET AL.
	Examiner Carla Myers	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 March 2007.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 41,43,48-51,54-57,60-63,67,70,73-76,79-81 and 86 is/are pending in the application.
- 4a) Of the above claim(s) 73 and 74 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 41,43,48-51,54-57,60-63,67,70,75,76,79-81 and 86 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____	6) <input type="checkbox"/> Other: _____

DETAILED ACTION

1. This action is in response to the amendment filed March 12, 2007. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 have been examined herein.

Claims 73 and 74 are withdrawn from consideration as being drawn to a non-elected invention. It is noted that Applicant elected invention I, claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86, without traverse in the reply filed on June 16, 2006.

New Grounds of Rejection

Claim Rejections - 35 USC § 112- New Matter

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 63, 67, 70 and 79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. Regarding claims 41 and 63, the specification as originally filed does not appear to provide support for the amendment to the claims to recite a nucleic acid (claim 41) or primer or probe (claim 63) consisting of a sequence of about the maximum number of nucleotides of the spacer region, wherein the nucleic acid, primer or probe does not include sequences of a tRNA gene. The specification (page 3) teaches that the spacer region comprises tRNA genes (i.e., "The 16S, 23S and 5S genes are separated by spacer regions in which transfer RNA (tRNA) genes and signal sequences involved in post-transcriptional processing may be found"). Thereby, a sequence that consists of the maximum number of nucleotides of a spacer region would also include tRNA gene sequences. While the specification provides support for the concept of a nucleic acid consisting of 15 to 100 nucleotides of the spacer region, wherein said nucleic acid does not include tRNA sequences, the specification as originally filed does not appear to provide support for the concept of a genus of nucleic acids consisting of a full length spacer region that does not include tRNA gene sequences.

B. Regarding claims 67 and 70, the specification as originally filed does not provide support for the concept of methods for detecting a prokaryotic microorganism by comparing the sequences of a nucleic acid to a database of known nucleic acid sequences. The response does not point to any particular teachings in the specification as providing support for this amendment. While the specification teaches a step of comparing nucleic acid sequences, the specification does not appear to teach the concept of comparing sequences to a database of known nucleic acid sequences.

C. Regarding claim 79, the specification as originally filed does not appear to provide support for the concept of a kit containing any agent for labeling amplified products. While the specification teaches primers and probes that are labeled, the specification does not appear to teach the concept of a kit containing any agent for labeling an amplified product.

Maintained Rejections

Claim Rejections - 35 USC § 112 – Written Description

3. Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The claims are inclusive of nucleic acids comprising sequences of a spacer region between the large subunit and small subunit rRNA of any prokaryotic organism, or the large subunit and the 5S subunit rRNA of any prokaryotic organism, or an RNA form thereof. The genus of prokaryotic is significantly extensive, including millions of highly diverse organisms, which differ substantially with respect to their nucleotide sequences. As detailed below, the claims do not define the nucleic acids in terms of their overall length, structure (e.g., nucleotide sequence), their specific source (i.e., a particular organism) or their specific function.

In particular, the claims are inclusive of “RNA forms” of a nucleic acid. This phrase is not defined in the specification and has been interpreted as including any RNA form of a nucleic acid sequence, wherein the RNA form may include any number and identity of nucleotide substitutions, and may include pre-processed versions of an RNA molecule or post-processed forms of an RNA molecule.

Claims 41, 43, 48 and 49 are drawn to nucleic acid molecules consisting of any 15 to 100 contiguous nucleotides obtained from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. While the claims recite that the nucleic acid is capable of detecting a species of a prokaryotic microorganism (claim 41) or hybridizes specifically to a target, the claims do not set forth any particular hybridization conditions. The phrase “hybridize specifically to a target” is not defined in the specification. For instance, this phrase has not been defined in the specification to be limited to oligonucleotides which hybridize to only one target (i.e., the target to which it is 100% complementary) and do not cross-hybridize to any other target, such as targets which share 99% complementarity. In the absence of a clear definition for this phrase, this phrase is not considered to further limit the structure or function of the oligonucleotides or the nucleic acid molecule comprising the oligonucleotides.

Claims 50, 51, 54 and 57 are drawn to methods which require the use of a probe consisting of any 15 to 100 contiguous nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. The spacer region is not defined in terms of any particular nucleotide

sequence and thereby may include probes consisting of tRNA genes. The claims do not recite any particular conditions of hybridization, do not recite the degree of complementarity shared between the probe and the target sequences and do not define the target sequences.

Claim 63 broadly encompasses any method of using a target nucleic acid wherein the target nucleic acid has a sequence of a maximum number of nucleotides of a spacer region. The claims state that the target nucleic acid is a primer or probe consisting of the maximum number of nucleotides of a spacer region, but do not clarify how the primer or probe can consist of the full length spacer region without including tRNA gene sequences. Further, claim 63 does not state how the target is used to detect a non-viral organism and do not define any probes or primers which would be used to detect a target region.

Claim 67 is drawn to methods for detecting a non-viral organism by amplifying nucleic acids using primers that consist of any 15 to 100 nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Claims 75-86 are drawn to kits comprising primers and probes of the same scope. The spacer region is not defined in terms of any particular nucleotide sequence or functional activity. The claims define the oligonucleotide in terms of its ability to hybridize specifically to a target. However, the specification does not provide a definition for the phrase "specifically hybridize" and there is no fixed definition in the art for this phrase. It is unclear from the teachings in the specification as to which nucleic acids the oligonucleotides hybridize with and which nucleic acids the

oligonucleotides do not hybridize with. Absence such a teaching, the language "specifically hybridizes" has been interpreted broadly and is not considered to impart any particular structural or functional limitations onto the oligonucleotides.

Claim 70 is drawn to methods which require the use of primers "derived" from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. The specification teaches that "rRNA gene spacer region derived" sequences refers to any probe that hybridizes to a spacer region. The conditions and specificity of hybridization are not defined. Accordingly, such sequences are given their broadest, most reasonable interpretation as encompassing spacer sequences which may include any number of nucleotide substitutions, deletions or additions. Thereby, the claimed primers are not considered to be defined in terms of a particular structure or length.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses the spacer sequences between the 16S rRNA and 23S rRNA of 10 prokaryotic microorganisms. The specification also exemplifies oligonucleotides from these spacer regions which can be used to distinguish between different species of the stated prokaryotic microorganism. For instance, the specification teaches oligonucleotides that can be used in a hybridization assay to distinguish between nucleic acids of *Neisseria meningitidis* and nucleic acids of *Neisseria gonorrhoeae*.

Accordingly, the written description requirement has been met for nucleic acid

probes and primers consisting of a sequence of a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, wherein the sequence consists of about 15 to about 100 contiguous nucleotides from a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, and wherein the probes or primers are species specific and do not include sequences of a tRNA gene.

However, the claims as very broadly written encompass nucleic acids, probes and primers obtained from any prokaryotic microorganism. Yet, the specification does not exemplify any probes or primers consisting of sequences of the spacer region between the 5S and large subunit rRNA genes. The specification does not teach a single nucleic acid, probe or primer containing spacer sequences from a tRNA sequence within the spacer region. Also, the specification does not exemplify any probes or primers containing sequences from regions other than the transcribed spacer region between the 16S and 23S rRNAs, as are included by the claims as broadly written to include any nucleic acid sequence (i.e., the claims which define the number of nucleotides, but not the identity of the nucleotides; those aspects of the claims directed to "RNA forms"; and claims directed to nucleic acids "derived" from a spacer region). Additionally, the specification teaches only nucleic acids, probes and primers which can be used to detect and/or distinguish between different species of prokaryotic microorganisms. The specification does not exemplify any nucleic acids having any other functional attributes.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the art teaches genomic sequences from other organisms, the specification provides no guidance as to how one may use particular sequences within the genomic sequences to obtain primers or probes for the detection of particular prokaryotic organisms. Given the substantial differences in the structure nucleic acid molecules from diverse organisms, the structure and function of one molecule does not provide guidance as to the structure and function of other molecules. Therefore, the description of 10 spacer regions between the 16S to 23S rRNA from prokaryotic microorganisms wherein the spacer region does not include tRNA sequences is not representative of the broadly claimed genus of any nucleic acid probe or primer comprising sequences of tRNA genes, or comprising sequences of the spacer region between the 5S to large subunit rRNA genes. A general statement in the specification of a desire to obtain spacer sequences and to use spacer sequences as probes or primers to detect organisms is not equivalent to providing a clear and complete description of specific sequences which fall within the claimed genus of nucleic acids. Accordingly, the specification does not disclose a representative number of species in terms of a specific structure or in terms of any other relevant, identifying characteristics.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

Art Unit: 1634

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. Additionally, *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed".

In the instant application, because of the limited amount of structural information or the complete absence of structural information regarding the claimed nucleic acid molecules, primers and probes, one of skill in the art cannot envision the detailed chemical structure of these nucleic acids, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acid sequences is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the broadly claimed genus of nucleic acid molecules, primers and probes, methods for using said nucleic acid molecules, primers and probes

or kits containing said nucleic acid molecules, primers and probes. Accordingly, it is concluded that the specification does not provide adequate written description for the claims as they are broadly written.

Response to arguments:

In the response of March 12, 2007, Applicants state that the claims have been amended to overcome the above grounds of rejection. In particular, it is stated that the probes which specifically hybridize are probes that do not cross-react with nucleic acids from other organisms and cite pages 1, 11, and 22-24 in support of this argument.

Applicants arguments have been fully considered but are not persuasive. The amendment to the claims to recite that the nucleic acid, primer or probe consists of or comprises sequences of the spacer region of prokaryotic microorganisms does not overcome all aspects of the written description rejection for the reasons set forth above. In particular, the claims encompass nucleic acid, primers and probes consisting of the spacer region between the large subunit and 5S subunit rRNA of any prokaryotic microorganism. However, the specification does not exemplify any nucleic acids, primers or probes meeting this criteria. The specification does not describe a representative number of species within this claimed genus in terms in terms of their complete chemical structure or other identifying characteristics. Additionally, the claims are inclusive of "RNA forms" of the nucleic acid, and as such, as discussed above, may include any number and identity of nucleotide substitutions, and may include pre-processed versions of an RNA molecule or post-processed forms of an RNA molecule. Claim 70 is inclusive of primers "derived" from a spacer region between the large

subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. The specification teaches that "rRNA gene spacer region derived" sequences refers to any probe that hybridizes to a spacer region. The conditions and specificity of hybridization are not defined and thereby, such sequences are given their broadest, reasonable interpretation as encompassing spacer sequences which may include any number of nucleotide substitutions, deletions or additions. Thereby, the claimed primers are not considered to be defined in terms of a particular structure or length or functional activity. Claims 63 and 70 also include primers consisting of tRNA sequences. However, the specification does not describe a representative number of primers consisting of tRNA sequences in terms of their overall structure or other specific structural and functional characteristics.

Regarding Applicants arguments that the specification teaches that probes that specifically hybridize do not cross with other organisms, the cited passages at pages 1, 11 and 22-24 do not support such an argument. The specification teaches the concept of preferred probes that are species specific. However, there is no definition provided in the specification to indicate that each of the claimed primers or probes or that primers or probes that "specifically hybridize" to a target do not cross-hybridize with sequences from other organisms. While the claims are read in light of the specification, limitations from the specification regarding preferred embodiments are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 112 – New Matter

4. Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the concept of immobilizing a primer to a solid support as is required by newly added claim 81. While the specification teaches the immobilization of probes to a solid support, wherein the probes are to be used in a probe hybridization assay, the specification does not appear to teach the concept of immobilizing primers onto a solid support.

Response to Arguments:

In the response, Applicants traversed this rejection. Applicants state that an oligonucleotide may be a primer or a probe. Applicants point to pages 42 and 45 of the specification as teaching that oligonucleotides (i.e., primers or probes) can be spotted at a known location on a solid support.

Applicants arguments have been fully considered but are not persuasive because the response mischaracterizes the teachings in the specification.

At page 42, the specification states that “one or more oligonucleotide **probes** are dot spotted on the membrane” (emphasis added). The specification also teaches “at least one of the **probes** according to the invention and specific for the microorganism(s) to be detected, which is dot spotted to a membrane” (emphasis added).

At page 45, the specification teaches “at least one **probe** selected among any of

those according to the invention and specific for *Neisseria gonorrhoeae*, which is fixed to a solid support" (emphasis added).

Accordingly, the specification teaches only the immobilization of probes. It is maintained that the specification does not provide support for the concept of immobilizing primers to a solid support.

Claim Rejections - 35 USC § 112 - Enablement

5. Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) isolated nucleic acid probes and primers consisting of a sequence of a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, wherein the sequence comprises about 15 to about 100 contiguous nucleotides from a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, and wherein the probes or primers are species specific and do not includes sequences of a tRNA gene, (ii) kits containing said probes or primers, and (iii) methods for detecting a prokaryotic microorganism using said probes or primers, does not reasonably provide enablement for nucleic acids, probes or primers comprising any eukaryotic or prokaryotic spacer region consisting of or derived from any region between a large subunit and small subunit of an rRNA gene or any other molecule or between the large subunit and 5S subunit of an rRNA gene, or comprising a sequence of any identity having the maximum number of nucleotides of a spacer region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in

scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are inclusive of nucleic acids comprising sequences of a spacer region between the large subunit and small subunit rRNA of any non-viral organism, or the large subunit and the 5S subunit rRNA of any non-viral organism, or an RNA form thereof. The genus of non-viral organisms is significantly extensive, including millions of highly diverse organisms, which differ substantially with respect to their nucleotide sequences. As detailed below, each of the claims do not define the nucleic acids in terms of their overall length, structure (e.g., nucleotide sequence), their specific source (i.e., a particular organism) or their specific function.

In particular, the claims are inclusive of “RNA forms” of a nucleic acid. This phrase is not defined in the specification and has been interpreted as including any RNA form of a nucleic acid sequence, wherein the RNA form may include any number and identity of nucleotide substitutions, and may include pre-processed versions of an RNA molecule or post-processed forms of an RNA molecule.

Claims 41, 43, 48 and 49 are drawn to nucleic acid molecules consisting of any 15 to 100 contiguous nucleotides obtained from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. While the claims recite that the nucleic acid is capable of detecting a species of a prokaryotic microorganism (claim 41) or hybridizes specifically to a target, the claims do not set forth any particular hybridization conditions. The phrase "hybridize specifically to a target" is not defined in the specification. For instance, this phrase has not been defined in the specification to be limited to oligonucleotides which hybridize to only one target (i.e., the target to which it is 100% complementary) and do not cross-hybridize to any other target, such as targets which share 99% complementarity. In the absence of a clear definition for this phrase, this phrase is not considered to further limit the structure or function of the oligonucleotides or the nucleic acid molecule comprising the oligonucleotides.

Claims 50, 51, 54 and 57 are drawn to methods which require the use of a probe consisting of any 15 to 100 contiguous nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. The spacer region is not defined in terms of any particular nucleotide sequence and thereby may include probes consisting of tRNA genes. The claims do not recite any particular conditions of hybridization, do not recite the degree of complementarity shared between the probe and the target sequences and do not define the target sequences.

Claim 63 broadly encompasses any method of using a target nucleic acid

wherein the target nucleic acid has a sequence of a maximum number of nucleotides of a spacer region. The claims state that the target nucleic acid is a primer or probe consisting of the maximum number of nucleotides of a spacer region, but do not clarify how the primer or probe can consist of the full length spacer region without including tRNA gene sequences. Further, claim 63 does not state how the target is used to detect a non-viral organism and do not define any probes or primers which would be used to detect a target region.

Claim 67 is drawn to methods for detecting a non-viral organism by amplifying nucleic acids using primers that consist of any 15 to 100 nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Claims 75-86 are drawn to kits comprising primers and probes of the same scope. The spacer region is not defined in terms of any particular nucleotide sequence or functional activity. The claims define the oligonucleotide in terms of its ability to hybridize specifically to a target. However, the specification does not provide a definition for the phrase "specifically hybridize" and there is no fixed definition in the art for this phrase. It is unclear from the teachings in the specification as to which nucleic acids the oligonucleotides hybridize with and which nucleic acids the oligonucleotides do not hybridize with. Absence such a teaching, the language "specifically hybridizes" has been interpreted broadly and is not considered to impart any particular structural or functional limitations onto the oligonucleotides.

Claim 70 is drawn to methods which require the use of primers "derived" from a spacer region between the large subunit and small subunit rRNA, the large subunit and

the 5S subunit rRNA, or an RNA form thereof. The specification teaches that "rRNA gene spacer region derived" sequences refers to any probe that hybridizes to a spacer region. The conditions and specificity of hybridization are not defined. Accordingly, such sequences are given their broadest, most reasonable interpretation as encompassing spacer sequences which may include any number of nucleotide substitutions, deletions or additions. Thereby, the claimed primers are not considered to be defined in terms of a particular structure or length.

Nature of the Invention:

The claims are drawn to isolated nucleic acids comprising sequences of a spacer region between small and large subunit rRNA genes. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F. 3d 1316, 1330 (Fed Cir. 2001).

The Teachings in the Specification:

The specification discloses the spacer sequences between the 16S rRNA and 23S rRNA of 10 prokaryotic microorganisms. The specification also exemplifies oligonucleotides from these spacer regions which can be used to distinguish between different species of the stated prokaryotic microorganism. For instance, the specification teaches oligonucleotides that can be used in a hybridization assay to distinguish between nucleic acids of *Neisseria meningitidis* and nucleic acids of *Neisseria gonorrhoeae*. Accordingly, the specification has enabled nucleic acid probes and primers consisting of a sequence of a transcribed spacer region between the 16S and

23S rRNA genes of a prokaryotic microorganism, wherein the sequence comprises about 15 to about 100 contiguous nucleotides from a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, and wherein the probes or primers are species specific and do not include sequences of a tRNA gene.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The specification teaches that the claimed nucleic acids are to be used as primers or probes to detect prokaryotic organisms and to specifically distinguish between different species of prokaryotic organisms. However, the prior art acknowledges the unpredictability of using nucleic acid sequences for the purposes of specifically detecting or distinguishing between species of organisms. Modification of even a single nucleotide within a sequence can significantly alter the hybridization specificity of a sequence. However, there is no specific disclosure provided in the specification as to particular nucleotides which are present in a representative number of internal transcribed spacer regions of prokaryotic organisms which are critical for maintaining the specificity of hybridization. It is thereby unpredictable as to how modifying the nucleic acid sequence of an internal transcribed spacer region, particularly, the spacer region between the 5S to 23S rRNA genes, by adding, deleting or substituting nucleotides will effect the functional activities of the resulting nucleic acid sequence. There is also no specific disclosure provided in the specification of alternative regions which can be predictably used to develop probes or primers for the detection of any prokaryotic organism. Thereby, it is also highly unpredictable as to

what other regions outside of internal transcribed spacer regions could be used to generate probes or primers for the detection of any prokaryotic organism.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably make and use nucleic acids probes and primers from the spacer region of the 5S to 23S rRNA genes. While one could generate an infinitely large genus of nucleic acids from the internal transcribed spacer region of prokaryotic organism or from other regions of any prokaryotic organism, analyze those sequences to determine which sequences are specific for a species and which sequences can be modified by adding nucleotides to the 5' and 3' terminus or by inserting, deleting or substituting any number and identity of nucleotides from within the sequence, and then assay each of the resulting nucleic acids to try to determine their biological activity and hybridization specificity, the outcome of such experimentation is highly unpredictable. The specification itself acknowledges that particular probe and primer sequences can only be identified by "trial and error" experimentation. However, providing methods for searching for additional nucleic acids and trying to determine the function of the resulting nucleic acid is not equivalent to teaching how to make and use specific nucleic acids.

Working Examples:

Again, the specification teaches the sequences of the internal transcribed spacer region for 10 prokaryotic microorganisms and exemplifies primers and probes from these regions which are useful to detect these particular prokaryotic microorganisms.

However, the specification does not provide any working examples of primers or probes consisting of the spacer region between the 5S to large subunit rRNA genes. Further, no working examples are provided of any primers or probes consisting of or comprising tRNA sequences or any primers or probes comprising any prokaryotic sequences from outside of the internal transcribed spacer region.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(l)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only 10 members of the genus of primers and probes comprising spacer sequences from prokaryotic organisms between the small subunit to large subunit rRNA genes, whereas the claims encompass a significantly large genus of nucleic acids, in which the overall structural and functional properties of the nucleic acids are not defined. In

particular, the specification does not teach any primers or probes consisting of the spacer region between the 5S and large subunit rRNA genes or consisting of sequences of tRNA genes. As set forth above, in view of the unpredictability in the art, extensive experimentation would be required to make and use additional nucleic acids because the specification does not provide sufficient guidance as to how to select the nucleotides which may flank these sequences, does not provide sufficient guidance as to how to modify these sequences by adding, substituting or deleting any number and identity of nucleotides, and does not provide sufficient guidance as to how to generate probes and primers from organisms which can be used for a practical purpose.

Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the broadly claimed invention.

Response to arguments:

In the response, Applicants traverse this rejection. The response states that above rejection does not apply to the claims as they have been amended. Applicants state that the specification describes the overall length of the probes and the source of the probes and teaches that probes that specifically hybridize do not cross react with nucleic acids from other organisms.

Applicants arguments have been fully considered but are not persuasive. The amendment to the claims to recite that the nucleic acid, primer or probe consists of or comprises sequences of the spacer region of prokaryotic microorganisms does not overcome all aspects of the enablement rejection for the reasons set forth above. In

particular, the claims encompass nucleic acid, primers and probes consisting of or comprising sequences of the spacer region between the large subunit and 5S subunit rRNA of any prokaryotic microorganism. However, the specification does not exemplify any nucleic acids, primers or probes meeting this criteria. The specification does not describe a representative number of species within this claimed genus in terms in terms of their complete chemical structure or other identifying characteristics and does not provide sufficient guidance to obtain such probes or primers and to use the probes and primers to specifically detect a prokaryotic microorganism.

Additionally, the claims are inclusive of "RNA forms" of the nucleic acid, and as such, as discussed above, may include any number and identity of nucleotide substitutions, and may include pre-processed versions of an RNA molecule or post-processed forms of an RNA molecule. Claim 70 is inclusive of primers "derived" from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. The specification teaches that "rRNA gene spacer region derived" sequences refers to any probe that hybridizes to a spacer region. The conditions and specificity of hybridization are not defined and thereby, such sequences are given their broadest, reasonable interpretation as encompassing spacer sequences which may include any number of nucleotide substitutions, deletions or additions. Thereby, the claimed primers are not considered to be defined in terms of a particular structure or length or functional activity. Claims 63 and 70 also include primers consisting of tRNA sequences. However, the specification does not describe a representative number of primers consisting of tRNA sequences in terms of their overall

structure or other specific structural and functional characteristics and does not provide sufficient guidance to enable the skilled artisan to make and use a representative number of these claimed primers and probes.

Regarding Applicants arguments that the specification teaches that probes that specifically hybridize do not cross with other organisms, the cited passages at pages 1, 11 and 22-24 do not support such an argument. The specification teaches the concept of preferred probes that are species specific. However, there is no definition provided in the specification to indicate that each of the claimed primers or probes or that primers or probes that “specifically hybridize” to a target do not cross-hybridize with sequences from other organisms. While the claims are read in light of the specification, limitations from the specification regarding preferred embodiments are not read into the claims.

See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 112 second paragraph

6. Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 41, 43, 48-51, 54-57, 60-63, 67, 75, 76, 79-81 and 86 are indefinite over the recitation of “RNA form.” This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. It is unclear, for example, as to whether this phrase refers to a RNA molecule that is identical to the claimed nucleic acid molecule except that it contains a U in place of T, or whether this phrase refers to pre-processed or post-processed RNA variants of the nucleic acid molecule. In the

absence of a clear definition for this term or a further characterization for this term in the claims, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Response to arguments:

In the response, Applicants state that the specification teaches that the probes or primers may consist of RNA or DNA. Applicants assert that one would thereby know that the term "RNA form" refers to the RNA molecule that is similar to the nucleic acid except that a T is replaced with a U in the RNA form.

This argument has been fully considered but is not persuasive. The above definition does not appear in the present specification and there is no clear definition in the art for the phrase "RNA form." Further, if such a definition did appear in the specification or in the claims, it would remain unclear as to what is meant by an RNA molecule that is "similar." For example, it is unclear whether such a molecule shares some unstated degree of complementarity or identity with a reference nucleic acid. If Applicant intends for this phrase to refer to only nucleic acids that differ in that they contain a "U" in place of "T," then the claims should be amended to recite this limitation.

B. Claims 43, 48 and 49 are indefinite over the recitation of "able to hybridize specifically to a target." This phrase is not defined in the specification and there is no specific art recognized definition for this phrase. It is unclear as to what is intended to be meant by "specifically hybridize." For example, it is unclear as to whether such nucleic acids hybridize only to SEQ ID NO: 1 (and thereby are fully complementary to SEQ ID NO: 1) or if such nucleic acids also hybridize with variants of SEQ ID NO: 1 (e.g.,

variants having 99%, 98%, 95%, 90%, 70% etc identity with SEQ ID NO: 1). In the later case, there are no specific teachings provided in the specification to indicate the cut-off point at which the nucleic acid no longer specifically hybridizes to SEQ ID NO: 1. If the claimed nucleic acid is capable of hybridizing with a nucleic acid that differs from SEQ ID NO: 1 by even 1 nucleotide, then such nucleic acids are not truly specific for SEQ ID NO: 1. Because the phrase "specifically hybridizes" is not clearly defined in the specification or art, one cannot determine the meets and bounds of the claimed subject matter. The claims also do not set forth the condition under which the oligonucleotides are "able" to hybridize. Accordingly, it is unclear as to how the recitation of "able to hybridize specifically to a target" is intended to further define the structure or function of the claimed oligonucleotides and the nucleic acid molecules comprising the oligonucleotides.

Response to arguments:

In the response, Applicants state that it is clear that "hybridize specifically" implies probes or primers that hybridize only to the prokaryotic organism being detected. This argument is not persuasive because the claims do not recite such a limitation and there is no clear definition provided in the specification for this phrase which limits the phrase to include only primers or probes that hybridize to only a specific target organism that is to be detected. Applicants point to page 26 of the specification as exemplifying a probe that hybridizes to *N. gonorrhoea*. However, this example provided in the specification is not equivalent to providing a clear and fixed definition for the phrase "hybridize specifically." Although the claims are interpreted in light of the

specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

C. Claim 63 is indefinite and vague because the claim does not set forth the essential method steps required to accomplish the objective of detecting an organism. The claims recite only a step of "using" a target, but do not recite how the target is used to accomplish the objective of detecting an organism.

Response to arguments:

In the response, Applicants state that the claim has been amended to recite using a target to detect a microorganism. However, this amendment does not clearly set forth the essential steps of the method because the claims as amended do not clarify

D. Claims 67 and 70 are vague and indefinite because the claims recite a step of comparing nucleic acid sequences and through the comparison step inferring the presence of a non-viral organism. However, the claims do not clarify how comparing nucleotide sequences to other unspecified nucleotide sequences allows for the detection of the presence of a non-viral organism.

Response to arguments:

In the response, Applicants state that this rejection has been overcome by amendment of the claims to recite that the sequences are compared to a database of known sequences. However, this amendment does not overcome the rejection. The claims do not set forth how the step of comparing sequences allows one to infer the presence of a prokaryotic microorganism. A comparison of nucleotide sequences does not result in the detection of the presence of a prokaryotic microorganism and the

claims do not recite the essential steps that allow for the detection of a prokaryotic microorganism.

New Grounds of Rejection:

E. Claim 41 is indefinite over the recitation of "is capable of detecting." Claims 29-35 are indefinite over the recitation of "capable of detecting." Capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited nucleic acids do in fact detect the microorganism or only have the potential to detect the microorganism under some unspecified conditions or following some unstated modification of the oligonucleotides. Amendment of the claim to read e.g. "...nucleic acid molecule probe which detects" would obviate this rejection.

F. Claim 63 is indefinite over the recitation of "at least one set of which" because this phrase lacks proper antecedent basis since the claim does not previously refer to sets of primers or probes.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,536,638. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a genus of probes which is inclusive of the probes claimed in '638. Specifically, the claims of '638 are drawn to probes of the of *N. gonorrhoeae* transcribed spacer region and consist of the sequences of any one of SEQ ID NO: 1-8 and methods of detecting *N. gonorrhoeae* using said probes. The instant claims are drawn to probes which comprise sequences of the internal transcribed spacer region, and particularly the sequences of *N. gonorrhoeae* of SEQ ID NO: 1-8 and methods for detecting *N. gonorrhoeae* using said probes. Thereby, the broadly recited probes of the instant invention are inclusive of the probes claimed in '638. Furthermore, the claims of '638 do not recite packaging the probes specific for the spacer region in a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made

to have packaged the probes of '638 in a kit for the expected benefits of convenience and cost-effectiveness for practitioners in the art wishing to detect *N. gonorrhoeae*.

8. Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 5,945,282. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '282 are drawn to probes comprising a sequence from a transcribed spacer region between the 16S and 23S rRNA of a prokaryotic microorganism and methods for detecting prokaryotic microorganism using said probes. The claims of '282 do not recite kits containing said probes and additional reagents for the detection prokaryotic microorganisms. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the ITS probes and reagents for hybridization and amplification in a kit for the expected benefits of convenience and cost-effectiveness for practitioners in the art wishing to specifically detect prokaryotic microorganisms.

9. Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-52 of U.S. Patent No. 6,277,577. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '577 both encompass probes comprising a sequence

from a transcribed spacer region between the 16S and 23S rRNA of a prokaryotic microorganism and methods for detecting prokaryotic microorganism using said probes.

10. Claims 41, 43, 48-51, 54-57, 60-63, 67, 70, 75, 76, 79-81 and 86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,656,689. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '689 both encompass probes comprising a sequence from a transcribed spacer region between the 16S and 23S rRNA of a prokaryotic microorganism, methods for detecting prokaryotic microorganism using said probes, and kits containing said probes.

Response to arguments regarding obviousness-type double patenting rejections:

In the response, Applicants traversed each of the above rejections by stating that the present claims are drawn to nucleic acids consisting of a sequence of the spacer region between the large subunit and the small subunit of rRNA genes of prokaryotic microorganism. It is asserted that this recitation is not recited in any of the patents which claim probes from a transcribed spacer region between the 16S and 23S rRNA genes.

This argument has been fully considered but is not persuasive. The response does not clearly explain the distinction between the presently claimed nucleic acids and the nucleic acids of claimed in the above cited patents. While the patents use the terminology of the 16S and 23S rRNA prokaryotic genes, those of skill in the art would recognize that the 16S rRNA gene refers to the small subunit rRNA gene, while the 23S rRNA gene refers to the large subunit rRNA gene. As stated at page 3 of the

specification, "In eubacteria the 16S rRNA gene [also called small subunit rRNA (srRNA)] is found at the 5' end of the rRNA cistron, followed by the 23S rRNA [also called large subunit rRNA(lrRNA)]. The 5S rRNA gene is located at the 3' end of the cistron. The 16S, 23S and 5S genes are separated by spacer regions in which transfer RNA (tRNA) genes and signal sequences involved in post-transcriptional processing may be found. "

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 50 is rejected under 35 U.S.C. 102(e) as being anticipated by Kohne (U.S. Patent 5,928,864; cited in the IDS).

Claim 50 is drawn to methods of detecting prokaryotic microorganisms using said probes wherein the probes consist of 15 to 100 nucleotides of the transcribed spacer region between the 16S and 23S rRNA. It has been interpreted that the claims are inclusive of probes consisting of sequences of the tRNA genes since the tRNA genes are present within the internal transcribed spacer region.

Kohne discloses and claims methods for detecting a microorganism present in a sample wherein the methods comprise contacting a sample nucleic acid with a probe and detecting hybridization of the probe to the sample nucleic acid as indicative of the presence of said microorganism. Kohne teaches that the probe consists of tRNA sequences which are specific for a particular organism (see, especially col. 3, 14 and 41-42) and states that a typical tRNA molecule is of a length of 75 to 85 bases (col. 2). Further, Kohne teaches that the probe may consist of precursor rRNA sequences (ps RNA) containing both spacer and rRNA sequences (see col. 19, 41-42 and 51). Kohne teaches that the probe is preferably a subsequence of the tRNA and ps RNA and that it may comprise 12 or more nucleotides and up to a thousand nucleotides (see col 19, and claim 1). The probe may be specific for a group of organisms, such as a genus or family, or may be specific for a particular species (see, e.g., claims 7 and 15). Kohne also teaches that tRNA and ps rRNA probes are generated by determining the tRNA or ps rRNA sequence of a target organism and the tRNA sequence or ps rRNA sequence of related organisms, comparing the sequences, and identifying unique sequences in order to design a probe specific for the target organism or group of organisms.

Further, Kohne teaches methods in which a target nucleic acid is contacted with a probe comprising sequences between the spacer region of rRNA under temperature and hybridization solution concentrations to allow for the formation of hybrids, wherein the formation of a hybrid infers the presence of an organism (see col. 14).

Response to arguments:

In the response, Applicants traverse this rejection. It is stated that Kohne teaches methods for detecting microorganisms using probes that consist of tRNA sequences. It is argued that Kohne does not teach methods using probes that do not have tRNA genes or precursor rRNA sequences.

This argument has been fully considered but is not persuasive because Applicants are arguing limitations that are not recited in the claim since claim 50 does not require the use of a probe that does not include a tRNA sequence.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of Saiki (PNAS. 1989. 86: 6230-6234; cited in the IDS).

The teachings of Kohne are presented above. Kohne does not teach immobilization of probes onto solid supports.

However, Saiki (page 6234) teaches "reverse dot blot" methods for detecting nucleic acids in which probes are immobilized onto a solid support and then contacted with a target nucleic acid. Saiki teaches that this method offers the advantages of being able to reuse the filter containing the immobilized probes and provides a method in which multiple probes with variations in the sequence can be employed in a single assay and the ability of these probes to hybridize with the target sequence can be readily ascertained because the location at which the probe is "dot-spotted" is known. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kohne so as to have immobilized the probes onto a solid support as taught by Saiki in order to have achieved the expected advantages expressly stated by Saiki of providing a detection assay which is economical, simple, robust and potentially automatable.

Response to arguments:

In the response, Applicants traverse this rejection. It is stated that Kohne teaches methods for detecting microorganisms using probes that consist of tRNA sequences. It is argued that Kohne does not teach methods using probes that do not have tRNA genes or precursor rRNA sequences.

This argument has been fully considered but is not persuasive because Applicants are arguing limitations that are not recited in the claim since claim 50 does not require the use of a probe that does not include a tRNA sequence.

13. Claims 51 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of White.

The teachings of Kohne are presented above. Kohne does not teach amplification of the target DNA by PCR prior to detection and particularly does not teach performing an amplification reaction using biotinylated primers or primers which hybridize to sequences of the 16S and 23S rRNA region.

However, White teaches methods for specifically detecting microorganisms in which primers complementary to conserved sequences in the large and small subunit rRNA region are used to amplify segments of the rRNA, including sequences of the internal transcribed spacer region. White teaches that the large and small subunit rRNA contain regions of high levels of sequence conservation, as well as regions of sequence variability. White teaches that primers may be obtained to the large and small subunit rRNA by identifying conserved sequences and teaches that such primers may be used to amplify sequences 3' and 5' to the large and small subunit rRNA, including sequences of the ITS region.

In view of the teachings of White, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of detection of Kohne so as to have amplified the target nucleic acid prior to detection in order to have achieved the benefit of increasing the quantity of the target nucleic acid

and thereby increasing the sensitivity of detection. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used primers complementary to conserved sequences of the 16S and 23S rRNA of prokaryotic microorganisms as the amplification primers in the modified method of Kohne in order to have provided an effective means for amplifying the ITS region containing tRNA sequences of prokaryotic microorganisms and thereby to have increased the quantity of the target prokaryotic nucleic acid and to have increased the sensitivity of detection of the target microorganism.

Response to arguments:

In the response, Applicants traverse this rejection for the same reasons stated above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

14. Claims 54, 55, and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of White and further in view of Saiki.

The teachings of Kohne and White are presented above.

The combined references do not teach labeling the primers and thereby the amplification products with a biotinylated moiety.

However, Saiki discloses a nucleic acid detection method wherein the target nucleic acid is amplified using biotinylated primers in order to generate a labeled amplification product which is subsequently contacted with a filter containing dot-spotted oligonucleotide probes. Hybridization of the labeled amplification product to the immobilized oligonucleotide probe is detected via the biotin moiety and is indicative of

the presence of the target nucleic acid. In view of the teachings of Saiki, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the detection method of Kohne so as to have amplified the target nucleic acid prior to detection using a biotinylated primer in order to have achieved the benefit taught by Saiki of facilitating the detection of hybridization between the amplification product and the probe.

Regarding claim 62, Kohne and White do not teach immobilization of probes onto solid supports.

However, Saiki (page 6234) teaches "reverse dot blot" methods for detecting nucleic acids in which probes are immobilized onto a solid support and then contacted with a target nucleic acid. Saiki teaches that this method offers the advantages of being able to reuse the filter containing the immobilized probes and provides a method in which multiple probes with variations in the sequence can be employed in a single assay and the ability of these probes to hybridize with the target sequence can be readily ascertained because the location at which the probe is "dot-spotted" is known. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kohne so as to have immobilized the probes onto a solid support as taught by Saiki in order to have achieved the expected advantages expressly stated by Saiki of providing a detection assay which is economical, simple, robust and potentially automatable.

Response to arguments:

In the response, Applicants traverse this rejection for the same reasons state above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634


CARLA J. MYERS
PRIMARY EXAMINER